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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,622	02/08/2000	HANS WERNER MULLER	P64029USO	6964

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/423,622	MULLER ET AL.	
	Examin r	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-61* is/are pending in the application.

4a) Of the above claim(s) *49,50,56 and 57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48, 51-55, 58-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *48-61* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority und r 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 26 August 2003 has been entered in full. Claims 1-47 are cancelled and claims 48-61 are added.

Claims 49-50 and 56-57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8 (21 September 2001).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 48, 51-55, and 58-61 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to claims 37-37 at pg 3-4 of the previous Office Action (24 February 2003) is *withdrawn* in view of the cancelled claims (26 August 2003). Please see section on Claim Objections, below.

2. The rejection of claims 36-38 and 42-47 under 35 U.S.C. § 112, first paragraph (scope of enablement) as set forth at pg 4-7 of the previous Office Action (24 February 2003) is *withdrawn* in view of the cancelled claims (26 August 2003). Please see section on 35 U.S.C. § 112, first paragraph, below.

3. The rejections of claims 36-38 and 42-47 under 35 U.S.C. § 112, second paragraph as set forth at pg 7-8 of the previous Office Action (24 February 2003) are *withdrawn* in view of the

cancelled claims (26 August 2003). Please see section on 35 U.S.C. § 112, second paragraph, below.

Claim Objections

4. Claims 48 are 55 objected to because of the following informalities:

4a. Claims 48 and 55 recite a non-elected species of inhibitor.

4b. Claims 51 and 58 (line 1) should recite "...is administered in combination..." rather than "...is administered n combination...". It appears to the Examiner that the "i" is missing in the word "in". Please note that this observation may or may not be due to the quality of the faxed amendment.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

5. Claims 48, 51-55, and 58-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of enhancing axonal regeneration comprising locally administering an inhibitor substance that inhibits basal membrane formation of the lesioned postcommissural fornix to enhance axonal regeneration, and wherein the inhibitor substance is an anti-collagen IV antibody or α, α'-dipyridyl (DPY), does not reasonably provide enablement for a method for enhancing axonal regeneration comprising specific inhibition of basal membrane formation induced by a lesion of neuronal tissue, the specific inhibition being effected by systemically or locally administering to a body in need thereof an inhibitor of basal membrane formation selected from the group consisting of an antibody against collagen IV, laminin, entactin, an inhibitor of an amino acid hydroxylase, and a combination thereof, thereby promoting recovery of CNS functionality. Furthermore, the specification, while being enabling for a method of treating lesioned postcommissural fornix, in which the lesion induces basal cell membrane formation, comprising locally administering to a body in need thereof, an inhibitor

substance that treats the lesioned postcommissural fornix, and wherein the inhibitor substance is an anti-collagen IV antibody or α, α'-dipyridyl (DPY), does not reasonably provide enablement for a method of treating a lesion of neuronal tissue, which lesion induces basal cell membrane formation, comprising by systemically or locally administering to a body in need thereof an inhibitor of basal membrane formation selected from the group consisting of an antibody against collagen IV, laminin, entactin, an inhibitor of an amino acid hydroxylase, and a combination thereof, thereby promoting recovery of CNS functionality. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth for claims 36-38 and 42-47 at pg 4-6 of the previous Office Action (24 February 2003).

The claims also recite that the inhibitor is administered in combination with a substance that stimulates neuronal growth. The claims recite the inhibitor is locally administered, intraventricularly, to the neuronal tissue. The claims also recite that the inhibitor is systemically administered, orally or intravenously. Finally, the claims recite that the inhibitor substance is administered in an amount of 1 ng/kg to 1 mg/kg body weight.

Applicant's arguments (26 August 2003) have been fully considered but are not found to be persuasive for the following reasons.

(i) Applicant asserts that the presently claimed invention teaches the use of compounds that inhibit formation of basal lamina in order to treat the neuronal damage--and accompanying loss of CNS functioning—caused by lesion in the nervous system, e.g. the severing of a nerve. Applicant contends that the attached Appendix is an experimental report showing the

extraordinary recovery of nerve-damaged rats following treatment in accordance with the presently claimed invention. Applicant explains that the fornix was damaged in a series of test rats, and in another series, the spinal cord was damaged. Applicant states that these experiments comprised both compartments of the CNS, i.e., the brain and the spinal cord, and focused in the axonal regeneration of two different cell types (i.e., fornix: limbic system fiber tract, non-motor tract; spinal cord: corticospinal tract, motor tract) to show the universality of response (i.e., axonal regeneration) with respect to cell type in the treatment of CNS lesions with basal-lamina formation inhibitors. Applicant submits that in each case, basal-lamina formation was effectively inhibited by local application of different iron chelators (2,2'-bipyridine, 2,2'-bipyridine-5,5'-dicarboxylic acid and desferrioxamine) and anti-collagen type IV antibodies. Applicant argues that for both brain lesion and spinal cord lesion paradigms, administration of basal lamina formation inhibitors (i.e, prolyl 4-hydroxylase inhibitors) resulted in axonal regeneration and associated recovery of CNS functioning. Applicant states that the recovery of functioning by regeneration in the fornix lesion is shown by electrophysiological improvement whereas the recovery of CNS functioning accompanying regeneration spinal cord is demonstrated by locomotion testing and by testing fine motor movements based on sensory coupling. Applicant indicates that two different neuronal cell types were tested (i.e., fornix: limbic system fiber tract, non-motor tract; spinal cord: corticospinal tract, motor tract) to show the universality of cell-type response to the treatment of CNS lesions with prolyl 4-hydroxylase inhibitors to prevent basal lamina formation. Applicant states that for the brain and spinal cord, it was shown that regardless of which neuronal cell types are involved in the lesion, basal lamina formation occurs after injury and that there is significant axonal regeneration as well as

behavioral improvement if basal lamina formation is prevented. Applicant asserts that the instant specification provides sufficient teaching to enable the skilled person to practice the invention as presently claimed. Applicant argues that it would have been readily understood by the skilled person that a successful axonal regeneration of damaged (lesioned) nerve tissue leads to the recovery of CNS functioning that had been lost due to the nerve damage suffered. Thus, no undue experimentation would have been required of the skilled artisan to determine useful inhibitors of basal cell membrane formation since classes of useful inhibitor compounds are expressly recited in the present claims.

Applicant's arguments have been fully considered but are not found to be persuasive. Although Applicant indicates an unpublished experimental report shows the recovery of nerve-damaged rats (fornix and spinal cord) following treatment in accordance with the presently claimed invention, Applicant's argument is not persuasive because the evidence in the unpublished manuscript must be submitted in the form of a declaration under 37 C.F.R. 1.132. An unpublished manuscript is not proper evidence, since it has not been peer-reviewed and its contents have not been attested to under 37 CFR 1.132. However, if submitted under 37 C.F.R. 1.132, the results in the experimental report would only be persuasive in part. As discussed by Applicant, the experimental report shows a reduction in basal lamina formation in the lesioned spinal cord and lesioned postcommissural fornix after administration of 5,5'-dicarboxylic acid derivative of 2,2'-bipyridine and desferrioxamine. Therefore, in view of the experimental report (if submitted under 37 CRF 1.132), the specification would still only be enabling for a method of enhancing axonal regeneration comprising specific inhibition of basal membrane formation induced by a lesion of neuronal tissue in the spinal cord and postcommissural fornix by local

administration of an inhibitor of membrane formation to enhance axonal regeneration, and wherein the inhibitor is an anti-collagen IV antibody, α,α'-dipyridyl, 5,5'-dicarboxylic acid derivative of 2,2'-bipyridine, or desferrioxamine. Also, in view of the experimental report (if submitted under 37 CRF 1.132), the specification would only be enabling for a method of treating lesioned postcommissural fornix and lesioned spinal cord, in which the lesion induces basal cell membrane formation, comprising locally administering to a body in need thereof, an inhibitor substance that treats the lesioned postcommissural fornix and lesioned spinal cord, and wherein the inhibitor substance is an anti-collagen IV antibody, α, α'-dipyridyl, 5,5'-dicarboxylic acid derivative of 2,2'-bipyridine, or desferrioxamine.

Additionally, although Applicant has amended the claims to recite classes of inhibitors of basal cell membrane formation, undue experimentation would still be required of the skilled artisan to test all possible inhibitors. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of the claim, then this great quantity of experimentation should be considered in the overall analysis". The specification only discloses a list of possible inhibitors of basal membrane formation (pg 3). This is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The skilled artisan must resort to trial and error experimentation to determine which class of compounds might yield one with the desired activity. Such trial and error experimentation is considered undue.

(ii) Applicant asserts that regarding administration of the inhibitor, the specification can satisfy the requirements for enablement without containing a single working example. Applicant states that whether there are working examples for administering the systemically, orally, and intravenously is of no moment, since one skilled in the art would have readily known how to perform such administrations. Applicant contends that the examples provided administer the inhibitor substances locally as a matter of convenience. Applicant indicates that deferoxamine, a well known approved drug for systemic administration in the treatment of thalassaemia is a non-protein inhibitor of basal lamina formation useful in the invention presently claimed.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action (24 February 2003), the specification of the instant application does not disclose administering the inhibitor substance systemically, orally, or intravenously. The specification (pg 6-12) and submitted experimental report teach that the inhibitor substances are administered locally to the lesioned fornix and spinal cord. Relevant literature reports that the goal of delivering drugs noninvasively has only achieved modest success, with poor applicability to proteins and peptides (pg 343, col 1-2; Pettit et al. Trends Biotechnol 16: 343-349, 1998). The problems posed by proteins and peptides is their large molecular size, electrical charge, relatively hydrophilic nature, and relative instability in environments of extreme pH or proteolytic activity (such as the stomach and intestine) (pg 343, col 2). Pettit et al. review several routes of protein administration and the limitations that have been encountered. For example, limited success has been achieved delivering proteins and peptides orally because of: 1) poor intrinsic permeability across intestinal epithelium, 2) susceptibility to enzymatic attack, 3) rapid post-absorptive clearance, and 4) chemical instability

(pg 344-345). Additionally, proteins or peptides administered systemically must resist clearance via molecular filtration by the kidney and clearance by the reticuloendothelial system (pg 345, col 2). Therefore, the state of the prior art establishes the unpredictability of delivering substances, such as proteins, to a subject. Although specific examples are not necessary to meet the requirements of 35 U.S.C. §112, first paragraph, undue experimentation would be required of the skilled artisan to administer an inhibitor substance systemically, orally, or intravenously to enhance axonal regeneration or to treat a lesion of neural tissue. There is little or no guidance in the specification regarding the quantity and duration of treatment if the inhibitor substance is to be administered via these routes. There is also no evidence in the specification or submitted experimental report to indicate that administration of an inhibitor systemically, orally, or intravenously is able to cross the blood brain barrier or enter the spinal column to inhibit basal membrane formation and enhance axonal regeneration. Applicant indicates that deferoxamine (desferrioxamine) is an approved drug for systemic administration in the treatment of thalassaemia. However, thalassaemia is a genetic form of anemia in which there is an abnormality of the globin portion of hemoglobin. In this particular *blood* disorder, desferrioxamine is not required to reach the brain or spinal cord and Applicant has not provided evidence indicating that it does. The claims of the instant application require that the inhibitor substance reach the brain and spinal cord to enhance axonal regeneration and treat lesioned neuronal tissue. The specification of the instant application only teaches the *local* administration of an anti-collagen IV antibody and α,α'-dipyridyl. However, this is not adequate guidance for the systemic, oral, or intravenous administration of an inhibitor substance, but is merely an invitation to the artisan to use the current invention as a starting point for further

experimentation. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily enhance axonal regeneration or treat a lesion of neuronal tissue via systemic, oral, or intravenous administration of an inhibitor of basal membrane formation.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to enhance axonal regeneration and to treat lesioned neuronal tissue, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to inhibition of basal membrane formation of the spinal cord, the complex nature of the invention, the unpredictability of axon regeneration and of the effects of delivering the inhibitor substance systemically, orally, or intravenously to a subject, and the breadth of the claims which fail to recite limitations on the region of the CNS and neuronal tissue treated/targeted, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

6. Claims 48, 51-55, and 58-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 48 and 55 specifically recite a method for enhancing axonal regeneration comprising specific inhibition of basal membrane formation induced by a lesion of neuronal tissue or a method of treating a lesion of neuronal tissue comprising systemically or locally administering a specific inhibitor of the basal membrane formation thereby promoting recovery of CNS functionality.

The specification as originally filed does not provide adequate written description for a method of administering a specific inhibitor of basal membrane formation to promote recovery of CNS functionality. It is not expressly asserted, nor does it flow naturally from the specification. Applicant has also not indicated in the response of 26 August 2003, the specific support that can be found in the specification for the promotion of recovery of CNS functionality.

35 USC § 112, second paragraph

7. Claims 48, 51-55, and 58-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. The term "being effected by" in claims 48 and 51-54 is a relative term which renders the claim indefinite. The term "being effected by" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear how specific inhibition is "being effected by" an inhibitor.

9. Claims 48, 51-55, and 58-61 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating that axonal regeneration is enhanced or a lesion of neuronal tissue is treated.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
29 October 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER